



Intraocular Lens Regulation

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Intraocular Lenses (IOLs)

- Cataract surgery
 - » >3 million performed per year in US and rising due to aging of population
 - » Most patients implanted with monofocal lens
- “Premium” intraocular lenses (IOLs) are intended to provide benefits beyond treating aphakia
 - » Multifocal, toric, accommodating, phakic
 - » 13% patients implanted with premium IOLs**
- All IOLs are Class 3 medical devices requiring premarket approval (PMA)

Monofocal IOLs

- 59 original PMAs approved
 - » Most PMAs have supplements with IOL modifications
→ hundreds of different lenses on the market
- FDA recognized ANSI/ISO standards provide recommendations on the preclinical requirements and clinical study design

“Premium” IOLs

- Currently approved “premium” IOLs
 - » 3 multifocals
 - » 1 accommodating
 - » 2 toric
 - » 2 phakic
- Many in the pipeline
 - » Phakic, aspheric, multifocal, toric, accommodative and combinations of the above including the first of a kind combination discussed at today’s meeting
- Incomplete group of recognized ANSI/ISO Standards for “Premium” IOLs

Ophthalmic Standards

- FDA working with the American National Standards Institute (ANSI) and the International Standards Organization (ISO) since the 1980's
- FDA Recognized Standards
 - » A consensus standard that FDA has evaluated and recognized for use in satisfying a regulatory requirement and for which FDA has published a notice in the Federal Register (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm>)
 - » 36 recognized ophthalmic standards

Recognized IOL Standards

- Preclinical requirements:
 - » ISO 11979 - 2, 3, 5, 6, 8
 - » ANSI Z80 – 7, 12, 13
- Clinical recommendations (study design, endpts, SPE* etc):
 - » Monofocal IOL (ANSI Z80.7, ISO 11979-7)
 - » Multifocal IOL (ANSI Z80.12, ISO 11979-9)
 - » Phakic IOL (ANSI Z80.13, ISO 11979-10)
- ISO TR 22979
 - » IOL modifications
 - » Defines “parent IOL”

* SPE (safety and performance endpoints): basic historical safety and effectiveness data (FDA Grid) incorporated in ISO 11979-7

Toric IOL Standards

- ANSI Z80.30-2010 - Awaiting recognition
 - » Clinical recommendations for aphakic:
 - **Study design** – controlled (lowest cyl) / uncontrolled
 - **Sample size** – min. 100 eyes
 - **Study Duration** – until rotational stability demonstrated
 - **Outcomes** – reduction of cyl, lens axis misalignment, visual disturbances, adverse event rates
 - **Performance criteria** – rotational stability (90% within 5° between visits 3 months apart), SPE
- ISO Draft 11979-7 - being revised to add toric

Accommodating IOL (AIOL) Standards

- ANSI Draft Z80.29 – begun 2004
- ISO Draft 11979-7 - being revised to add AIOL
- ANSI & ISO Common Elements
 - » **Study design** – two phases
 - » **Sample size** – AIOL (min 300 eyes); Control (min 122 eyes)
 - » **Study Duration**
 - » **Performance criteria**
 - $\text{avg} \geq 1 \text{ D obj. accommodation}$ (Phase 1 & 2)
 - SPE (Phase 1 & 2)
 - No statistically significant decrease in objective accommodation over 6 months (Phase 2)

AIOL Standards: Outcomes

- Contrast sensitivity
- Visual disturbances
- Adverse event rates
- Objective Accommodative Amplitude
 - » Min. 100 AIOL; 50 control
 - » Assess at 6 month intervals until stability demonstrated (up to 3 years)
 - » Optical methods (ISO)
 - » Optical or Biometric methods (ANSI only)

P030002/S027

Trulign Toric Accommodating Posterior Chamber Intraocular Lens

Introduction

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Engineering

Patient Labeling

Bioresearch Monitoring

Microbiology

Clinical

Team Leader/Biocompatibility

Software Validation

Statistics

Clinical

Epidemiology/Literature Search

MDR Search

Bausch + Lomb

Trulign Toric Accommodating IOL

- First of a kind
 - » Combination of toric and accommodative features

Rationale for Meeting

- To solicit Panel's opinion on:

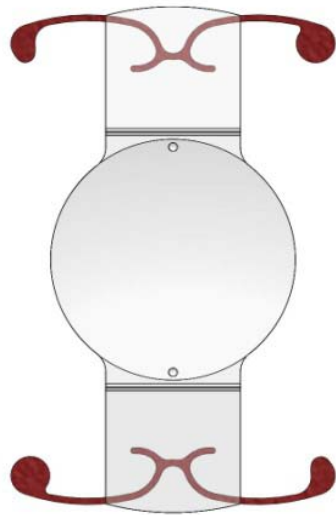
The safety and effectiveness of the Trulign Toric Accommodating Posterior Chamber Intraocular Lens (IOL) for the proposed indications for use

Proposed Indications for Use

The Trulign Toric Accommodating Posterior Chamber Intraocular Lens is intended for primary implantation in the capsular bag of the eye for the visual correction of aphakia and postoperative refractive astigmatism secondary to removal of a cataractous lens in adult patients with or without presbyopia who desire improved uncorrected distance vision and reduction of residual refractive cylinder. The Trulign Toric Accommodating Posterior Chamber Intraocular Lens provides approximately one diopter of monocular accommodation, which allows for near, intermediate, and distance vision without spectacles.

Device Description

- IOL



- Web Based Toric Calculator

Device Description

- IOL
 - » Plate haptic lens with hinges across the plates near the optic
 - » Biconvex silicone optic with toric posterior surface, polyimide loops
 - » Axis marks on the anterior surface, indicating the flat meridian of the optic
 - » 5.0mm optic, 11.5mm overall diameter
 - 12.0mm diameter also requested

Device Description

- Web Based Toric Calculator
 - » Accessed via internet
 - » Recommends IOL cylindrical power and placement axis using
 - Preoperative keratometry
 - Phaco/insertion incision location
 - Estimated magnitude of surgically induced astigmatism (SIA)

Preclinical Studies

- Optical / mechanical
- Biocompatibility
- Sterilization
- Packaging and Shelf-Life
- Manufacturing
- Software Validation (toric calculator)

Crystalens Accommodating IOL
Model AT-45 - 4.5mm optic
P030002 - Approved Nov. 2003



Crystalens Accommodating IOL
Models AT-50SE/AT-52SE - 5.0mm optic
P030002/S010 - Approved July 2007



Trulign Toric Accommodating IOL
Models AT-50T/AT-52T - 5.0mm toric optic
P030002/S027 - Filed May 2012



Crystalens HD
Models AT-45-HD100/HD500/HD520
Aspheric button, 5.0mm optic
P030002/S014 - Approved June 2008

Regulatory History

- G990163/S023 (Nov. 2004)
 - » Original toric IOL (AT-45T) study (Protocol ARL-55T)
- G990163/S036 (May 2007)
 - » Study suspended
 - » Two reports of unanticipated adverse events
 - Failure to show expected reduction in refractive cylinder
 - Explanation of both subjects
- G990163/S046 (May 2009)
 - » Pilot study approved
 - » Assessment of corrective actions, Model AT-45T (Protocol 612)

Regulatory History

- G990163/S049 (April 2010)
 - » Pivotal study approved
 - » Study of Model AT-50T (Protocol 650)
- P030002/S027 (May 2012)
 - » PMA Supplement filed
 - » Subsequent amendments rec'd
 - Nov. 2012 – FDA executive summary/presentation

P030002/S027

Trulign Toric Accommodating Posterior Chamber Intraocular Lens

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FDA/CDRH/ODE

April 8, 2013

Proposed Indications for Use

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Protocol #650

- Study IOL: Model AT-50T (Trulign)
 - » 11.5 mm
 - » Toric Calculator used to determine cylinder power (1.25D, 2.00D, or 2.75D)
- Control IOL: Model AT-50SE (Crystalens)
 - » 11.5 mm
 - » Spherical IOL

Study Design (Protocol #650)

- Prospective
- Multicenter (9 sites)
- Single-masked
- Partially randomized/controlled
- Monocular Implantation
- Follow-up based on establishment of rotational stability (max 1 year)

Study Design

Study Groups (c/w current ANSI TIOL):

- Randomized With Control
 - » 1.25 D toric model only
 - » Eyes randomized to toric or spherical analog
 - » Subjects masked to implanted IOL type
- Non-Randomized Without Control
 - » 2.00 D and 2.75 D toric models

Primary Effectiveness Endpoints*

- Percent reduction in absolute cylinder*
 - » Expressed as a % of the intended reduction in cylinder
- Percent of eyes with “reduction of cylinder”*
 - » Within 0.50 D and within 1.00 D of intended
- Lens axis misalignment
 - » As determined by a photographic method

* Evaluated when rotational stability achieved (i.e., Form 4 or 4-6 months post-op)

Secondary Effectiveness Endpoints

- Uncorrected Visual Acuity (UCVA)
 - » Distance (UCDVA)
 - » Intermediate (UCIVA)
 - » Near visual acuity (UCNVA)
- Distance corrected VA (DCVA)
 - » Best Corrected Distance Visual Acuity (BCDVA)
 - » Intermediate visual acuity (DCIVA) - 32 inches (80 cm)
 - » Near visual acuity (DCNVA) - at 16 inches (40 cm)
 - With and without the minimal reading add

Safety

- No Primary Safety Endpoint was specified due to the expectation that the safety profile of the Trulign IOL would be similar to that of the Crystalens IOL, based on IOL design
- Endpoints
 - » Preservation of BCVA (distance and near)
 - » Incidence of complications and adverse events

Surgical Procedure – Key Points

- Bilateral implantation not permitted
- Recommendations to prevent forward vaulting
 - » Incision width of < 3.0 mm and 1.5 mm paracentesis
- Incision at steep axis (pre-op keratometry)
- Sutures avoided
- No corneal or refractive procedures permitted
 - » E.g. limbal relaxing incisions or astigmatic keratotomies
- Type of incision (clear corneal, limbal, or scleral)
 - » Surgeon Decision
 - » Recorded on CRF

Assessments/Methodology

- No objective or subjective measures of accommodative amplitude
 - » Believed to be comparable to Crystalens
 - » PMA concern:
 - potential need for accommodative assessments
- Lens axis position was assessed through image capture with registration to ocular landmarks

Enrollment

229 subjects* enrolled at 9 sites (1 in Canada):

- 158 subjects - randomized group
 - » 82 in the toric 1.25 D arm
 - » 76 in the control arm (spherical IOL)
- 71 subjects - non-randomized group
 - » 47 toric 2.00 D subjects
 - » 24 toric 2.75 D subjects

*monocular study, hence # subjects = # eyes

Accountability

- 229 Subjects Enrolled
 - » 2 subjects discontinued before implantation due to surgical complications
 - » 1 subject discontinued after implantation (withdrew consent one day after surgery)
 - » 15 subjects still active when the PMA was submitted
- 211 Subjects available for analysis at Form 4

Total Protocol Deviations

At the time of Amendment 4 - 401

- » Major – 28*
- » Minor – 373*

*Four minor deviations were reclassified to major protocol deviations during review of the application (through Amendment 4), but were not included in the information presented in the FDA executive summary.

Major Protocol Deviations (28/401)

- 11 Failure to Meet Enrollment Criteria
 - » BCVA eligibility criteria
 - » Chronic steroid use
 - » Amblyopia
 - » Corneal astigmatism measurement by topography and (correct) keratometry differed by >0.50D using vector analysis
- 7* Noncompliance with the Surgical Protocol
 - » 3 Study IOL implanted after anterior/posterior capsular tear
 - » 4* Corneal incision at position different from that stated in the protocol (>10 degrees off axis)
- 10 Implanted with AT-52T/AT-52SE IOLs

*Four minor deviations were reclassified to major protocol deviations during review of the application (through Amendment 4), but were not included in the information presented in the FDA executive summary.

Minor Protocol Deviations (373/401)

- 151 Protocol Assessments Not Performed
 - » E.g., Visual acuity measurements not done, Surgical video or post-operative photos not captured, etc.
- 101 Protocol Procedures/Assessments Done Incorrectly/Incompletely
 - » E.g., Visual acuity measurements used different methodology than protocol, etc.
- 82 Documentation Practices
 - » E.g., Site completion of the Subject Questionnaire Case Report Forms (CRFs) for the subjects, CRF completed using subject completed source
- 22 Out of Window Visits
- 15 Informed Consent Issues
 - » E.g., Consent Process Deviations
- 2 Missed Visit

Question for Panel Discussion

Given the conduct of the study (i.e., over 400 protocol deviations ranging in severity from implantation of an unapproved device model to poor documentation practices), do you believe that the data generated are able to demonstrate that the benefits from the Trulign Toric Accommodating IOL outweigh the risks?

Safety Results: All Toric Eyes

BCVA \geq 20/40

- BCDVA of 20/40 or better
 - » 97.9% (139/142 eyes) at Form 4
- BCNVA of 20/40 or better
 - » 100% (142/142 eyes) at Form 4

Safety Results: Adverse Events (AE)

- ISO SPE Adverse Events (“FDA Grid”)
 - » Cumulative
 - » Persistent
- Surgical Adverse Events
- Ocular Adverse Events
- Non-Ocular Adverse Events

Cumulative Adverse Events

All Toric Eyes (151 eyes)

- » Macular edema - 0.7% (1 cumulative AE)
- » Secondary surgical intervention - 0.7% (1 cumulative AE)

Control Eyes (76 eyes)

- » Macular edema -1.3% (1 cumulative AE)
- » Secondary surgical intervention - 1.3% (1 cumulative AE)

Secondary Surgical Intervention (Study Eyes – Toric and Control)

2 cases:

- » One eye implanted with the Toric 2.00 D IOL
 - IOL vaulting at the Form 4 visit

- » One eye implanted with the Control IOL
 - IOL malposition at postoperative day one

Ocular Serious Adverse Events (Study and Non-Study Eyes)

- 2 cases of vaulting
 - » 1 eye implanted with the Toric 2.00 D IOL
 - » 1 non-study fellow eye implanted with Crystalens IOL
- 1 case of IOL malposition
 - » Superior haptic placed in the capsular bag and the inferior haptic placed in the sulcus
 - » Control eye

Applicant Definition of Anterior Vault*

“The Crystalens is designed to vault forward with ciliary muscle contraction when focusing at near and return to its original position with ciliary muscle relaxation when focusing at distance. The ‘anterior vault’ listed as an adverse event does not refer to this expected movement of the Crystalens, but rather to the condition that occurs when the lens optic becomes lodged in an anterior position independent of ciliary muscle relaxation or contraction, that is, whether the patient is focused at distance or at near.”

*From Amendment 4

Applicant Definition of Z syndrome*

“...an asymmetric combination of capsular contraction forces and vitreous pressure can result in the anterior vault of one hinge and the posterior vault of the other hinge. This creates an asymmetric tilt of the Crystalens, also known as ‘Z-Syndrome’.”

*From Amendment 4

Definition of Z Syndrome in Literature

“Asymmetric vault is a postoperative complication unique to the accommodating Crystalens IOL. Because of irregular capsule contraction, 1 haptic is pulled anteriorly while the other remains in the normal posterior position. The IOL configuration in the capsular bag resembles the letter Z, with the tilted optic in the middle.”*

*Jardim D, Soloway B, Starr C. Asymmetric vault of an accommodating intraocular lens. J Cataract Refract Surg. 2006 Feb;32(2):347-50.

Vaulting: 2 Cases in Trulign Study (Form 4)

- Trulign IOL
 - » Noncompliance with medications
 - » IOL repositioned, resultant IOL axis misalignment of 56.84 degrees
- Crystalens IOL (fellow eye)
 - » Zonular dehiscence
 - » IOL repositioned, explanted, and implantation of another Crystalens IOL attempted then aborted

Anterior Vault: Crystalens IOL (AT-45)

- Original pivotal study (324 subjects / 497 eyes)
 - » 1 case of IOL explantation due to vault
- Labeling
 - » Anterior vault identified as an adverse event and precautions included
- After approval, additional vaulting cases
 - » Labeling changes (9/26/05) to mitigate:
 - Larger capsulorrhexis size (5.5-6.0 mm rather than 5.0-5.5 mm)
 - Meticulous cortical clean-up and IOL rotation at least 90° to dislodge any hidden or trapped cortex
 - Tapering course of anti-inflammatories (min. 4 wks)

Additional Vaulting Assessment

- Medical Device Reports (MDRs) to FDA
 - » Conducted by Division of Postmarket Surveillance/
Office of Surveillance and Biometrics
- Published Literature Review

Medical Device Reporting System

- A nationwide passive surveillance system
- Manufacturer and User Facility Device Experience (MAUDE) Database
 - » Mandatory
 - Manufacturers and importers
 - User facilities
 - » Voluntary reporting (MedWatch)
 - Healthcare providers
 - Consumers

Limitations of MDRs

- Under-reporting
- Data quality issues
- Inability to determine rate
- Biased information
- Inability to determine causality

Methodology – MDR MAUDE Search

- Search Criteria:
 - » Brand Name: “Crystalen”
 - » Date Entered: < January 25, 2013

Search Results

Total Number of MDR Reports – 1,268

- Proportion by Report Source
 - » Manufacturers (1,248) 98%
 - » Voluntary (20) 2%
- Types of Events
 - » 1,106 injuries 87%
 - » 162 malfunctions 13%

Number of Reports Received by Year

Year	Number of Reports
2004	27
2005	23
2006	39
2007	309
2008	256
2009	183
2010	167
2011	154
2012	101
2013 (till Jan 25)	13

Categorization of the MDRs

- Vaulting -----153
- Positioning Issues ----- 46
- Z-Syndrome ----- 36
- Capsular Contraction ----- 30
- Tilting ----- 6

Total

271

Findings from Review of the MDRs

Other Categories of Complications Include:

Lens Damage (Haptic breakage) -----	596
Vision Disturbances -----	214
Capsular Bag Tear -----	86
Insertion Issues (Delivery) -----	15
Miscellaneous-----	86

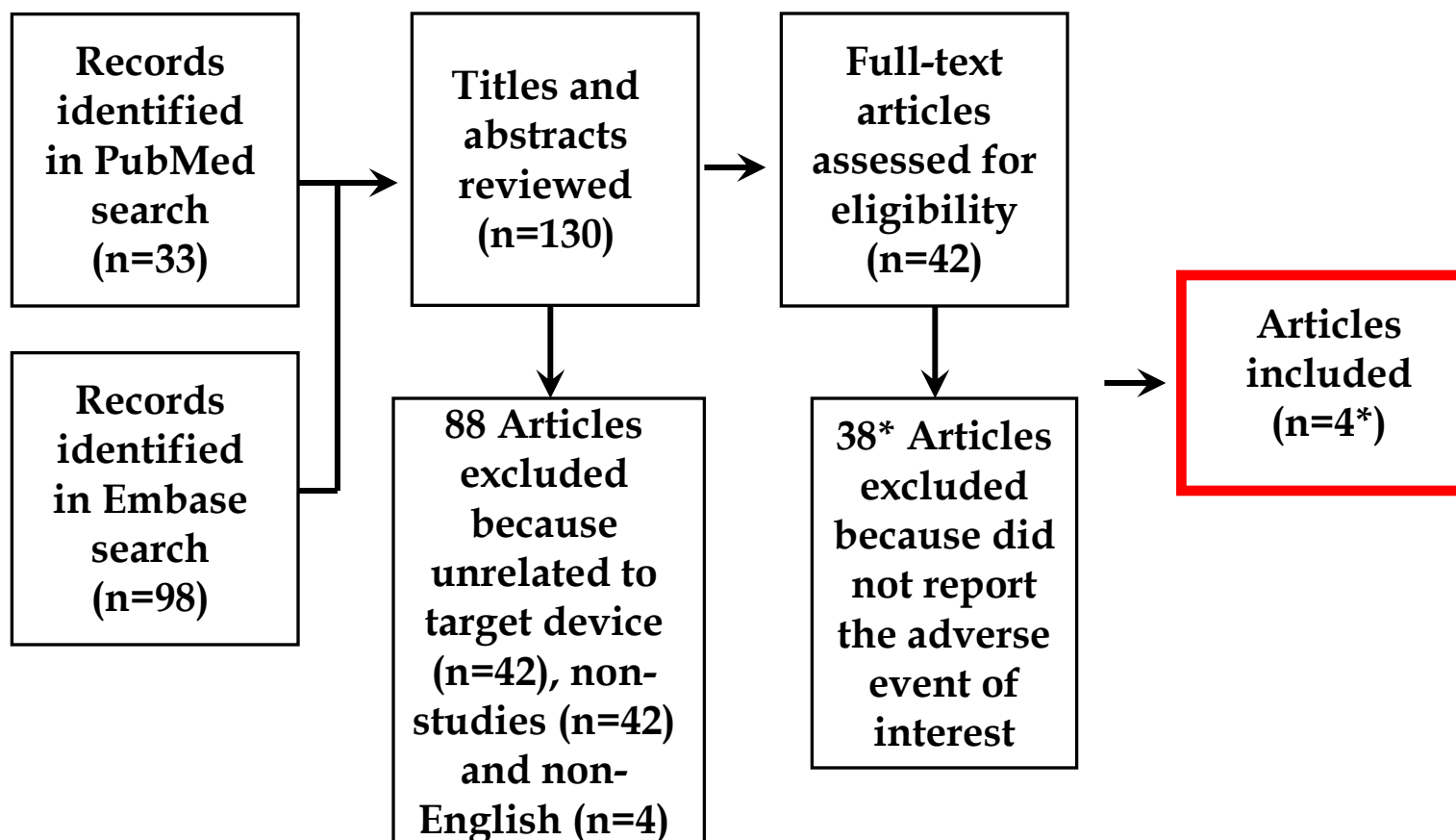
Additional Vaulting Assessment

- MDR reports to FDA
- Published Literature Review
 - » Performed by Division of Epidemiology, Office of Surveillance and Biometrics

Background and Methods

- Systematic literature review to address anterior vaulting as a unique safety concern of Crystalens
- Databases: EMBASE and PUBMED
- Search Terms: 'crystalens' and all model names
- Limited to Human studies in English between 2000 and 2012

Vaulting Article Retrieval and Selection



* Note this is a change from the numbers in the executive summary as six articles included in the original analysis did not report the adverse event of interest and includes an additional case report.

Vaulting Search Results

Author, Year	Study Design	N	Location	Major Findings
Cazal, 2005	Case report	1 eye	Spain	Lens tilting noted at 3-week follow up appeared to be caused by equatorial capsular fibrosis around the polyimide haptics with capsular contraction
Jardim, 2006	Case report	1 eye	US	Late asymmetric vault, occurring 6 months after implantation
Yuen, 2008	Case report	2 eyes	US	Vertically tilted Crystalens found at 6 weeks postop visit
Kim, 2008	Chart Review	1 eye	Korea	Asymmetric vaulting noted at 1 month postop

Vaulting – Available Information

- Pivotal Study Data:
 - » 2 case reports in the current pivotal study (229 subjects)
 - » 1 case of IOL explantation due to anterior vault in the original approval study for the Crystalens IOL (324 subjects/497 eyes)
- MDR data:
 - » 1268 total MDRs
 - » Approximately 271 related to vaulting (Vaulting, Capsule Contraction, Z-Syndrome, Tilting, and Positioning)
- Literature Review
 - » Limited discussion related to the issue of vaulting
 - » 5 subjects (3 case reports and 1 retrospective chart review) with severe lens tilt, vault change, or z-syndrome from capsular fibrosis.
 - » Limitations include variable language/terms to describe the event

Question for Panel Discussion

The following information is available regarding vaulting:

- » Trulign Toric Accommodating IOL
 - 2 reports in the P030002/S027 clinical study
- » Crystalens Accommodating IOL
 - 1 report in P030002 clinical study
 - Approximately 270 MDRs potentially related to vaulting
 - 5 cases in the literature

In light of this information, do you believe the data support reasonable assurance of safety of the Trulign Toric Accommodating IOL?

Effectiveness: Percent Reduction in Cylinder

- Percent Reduction of Cylinder = Achieved/Intended
 - » Achieved = |Postop Manifest Refractive Cylinder| –
|Preop Keratometric Cylinder|
 - » Intended = |Intended Postop Manifest Refractive Cylinder| –
|Preop Keratometric Cylinder|
 - Intended Reduction of Cylinder includes 0.5 D Surgically Induced Astigmatism
 - Based on Inclusion Criteria, There Were No Intended Overcorrections

Primary Effectiveness Endpoints Results – AT-50T

	Sphere	1.25 D	All Toric
Percent Reduction in Cylinder, mean	45.4	81.2	85.6
Percent Reduction in Cylinder, p-value		<0.001	
% of Eyes with Reduction in Cylinder within 0.50 D of intended	45.3	79.7	79.1
% of Eyes with Reduction in Cylinder within 1.00 D of intended	70.3	95.7	95.3
Absolute Value of Lens Axis Misalignment From Surgical Markings, mean	N/A	3.3	3.0

Rotational Stability (Form 3 – Form 4)

- Both mean and median absolute rotation at Form 4 in all eyes implanted with a toric IOL were approximately 1 degree.
- Approximately 99% of the eyes in the analysis showed rotation of ≤ 5 degrees.

Secondary Effectiveness Endpoint Results: Mean Uncorrected Visual Acuities

	Toric IOL (1.25 D)	Spherical IOL (control)	P value
Distance Uncorrected VA	0.096	0.185	0.004
Intermediate Uncorrected VA (80 cm)*	0.042	0.071	0.465
Near Uncorrected VA (40 cm)	0.288	0.285	0.947

*Revised from executive summary to reflect Amendment 4

Mean Uncorrected Visual Acuities Adjusted for Residual Spherical Error (Form 4)

Improvement in Logmar Acuity in 1.25 D Toric vs.
Control:

- Δ UCDVA: 0.069 ($p = 0.004$)
 - » 2/3 line
- Δ UCIVA: 0.037 ($p = 0.053$)
 - » 2 letters
- Δ UCNVA: 0.018 ($p = 0.403$)
 - » 1 letter

Monocular UCNVA \geq 20/40

- Trulign Toric IOL (all cylinder powers) 70.7%
 - » Trulign Study
 - Subjects with 1.33 D - 3.0 D corneal astigmatism
 - » Form 4 (4-6 months postoperatively)
- Crystalens AT-45 89.1%
 - » Original Spherical IOL Study Primary Eyes
 - Subjects with \leq 1.00 D corneal astigmatism
 - » 1 year postoperatively

Spectacle Independence

- Trulign IOL Study (Monocular)
 - » Not assessed as a formal endpoint
 - » Visual disturbances questionnaire
 - Not validated
 - Included 1 question specific to spectacle independence
 - Frequency of Glasses Wear: None of the Time*: 32.3% control, 30.4% Toric 1.25 D, 32.3% all Toric
- Crystalens IOL Study (Bilateral)
 - » Included a questionnaire
 - Not validated
 - No control
 - Multiple Assessments of Spectacle Independence
 - I do not wear spectacles: 25.8%
 - I wear spectacles almost none of the time: 47.7%

Question for Panel Discussion

Spectacle Independence was not assessed as a formal endpoint in the Trulign monocular study. At Form 4, 70.7% of toric IOL implanted eyes achieved UCNVA \geq 20/40, and 97.7% of toric IOL implanted eyes achieved UCIVA \geq 20/40. The proposed indications for use states that the “...Trulign Toric provides approximately one diopter of monocular accommodation which allows for near, intermediate and distance vision without spectacles.” Do the available data support the proposed indications for use?

DCNVA \geq 20/40

» Trulign Toric Study (Form 4)

- 62.9% Trulign Toric IOL (all cylinder powers)*
- 64.6% Crystalens AT-50SE/AT-52SE (control, spherical IOL)

» Original Spherical IOL Study (12 mo postop)

- 90.1% Crystalens AT-45

*includes both AT-50T/AT-52T

Crystalens Accommodation: Mechanism of Action

- Crystalens Labeling States:

“The Crystalens® was designed to move in a backward and forward motion along the axis of the eye in response to pressure changes in the vitreous cavity and anterior chamber that result from relaxation and contraction of the ciliary muscle. The exact mechanism of action has not been fully elucidated.”
- Speculation has been made in literature that part of the mechanism of action of the Crystalens is not due to a true overall focal shift, but to increased aberrations or astigmatism (from tilt) related to ciliary muscle contraction*

*Dell SJ. Pilocarpine-induced shift of an accommodating IOL. J Cataract Refract Surg. 2005 Aug;31(8):1469-72; author reply 1472-5.

Accommodative Amplitude (AA)

- Trulign IOL
 - » No assessment in this study (Study #650)
 - During IDE, future PMA concern communicated
 - Potential need for accommodative assessments
- Crystalens IOL
 - » Accommodative ability likely comparable
 - Based on similarity of IOL designs

Accommodation Data Available from Crystalens AT-45 PMA

- Study demonstrated improved levels of intermediate and near acuity, compared to a standard monofocal IOL
 - » Does not necessarily indicate functional accommodation
 - » Acuity can be influenced by many non-specific factors:
 - blur interpretation
 - corneal multifocality
 - depth of focus related to IOL aberrations
 - pupil size
- 5 subjects (10 eyes) at a single site underwent additional testing to document the mechanism of action

Accommodation: Crystalens HD (Supplement 14)

- 35 eyes (31 primary; 4 fellow) from 2 clinical sites
- Change in Anterior Chamber Depth (ACD) tested:
 - » ACD measured by Quantel Immersion Biometry, A Scan
 - » IOL movement: 1% cyclo ACD - 6% pilo ACD
 - 0.62 mm mean in 31 primary eyes (range: -0.9 to 1.6 mm)
 - » IOL movement: unmedicated baseline ACD – s/p 6% pilo ACD
 - 0.23 mm mean in 31 primary eyes (range: -0.7 to 0.8 mm)
- Push Down Test in 33 eyes
 - » MN Read Card
 - » Concluded mean value of 3.93 D (range 2.63 D to 10.00 D)

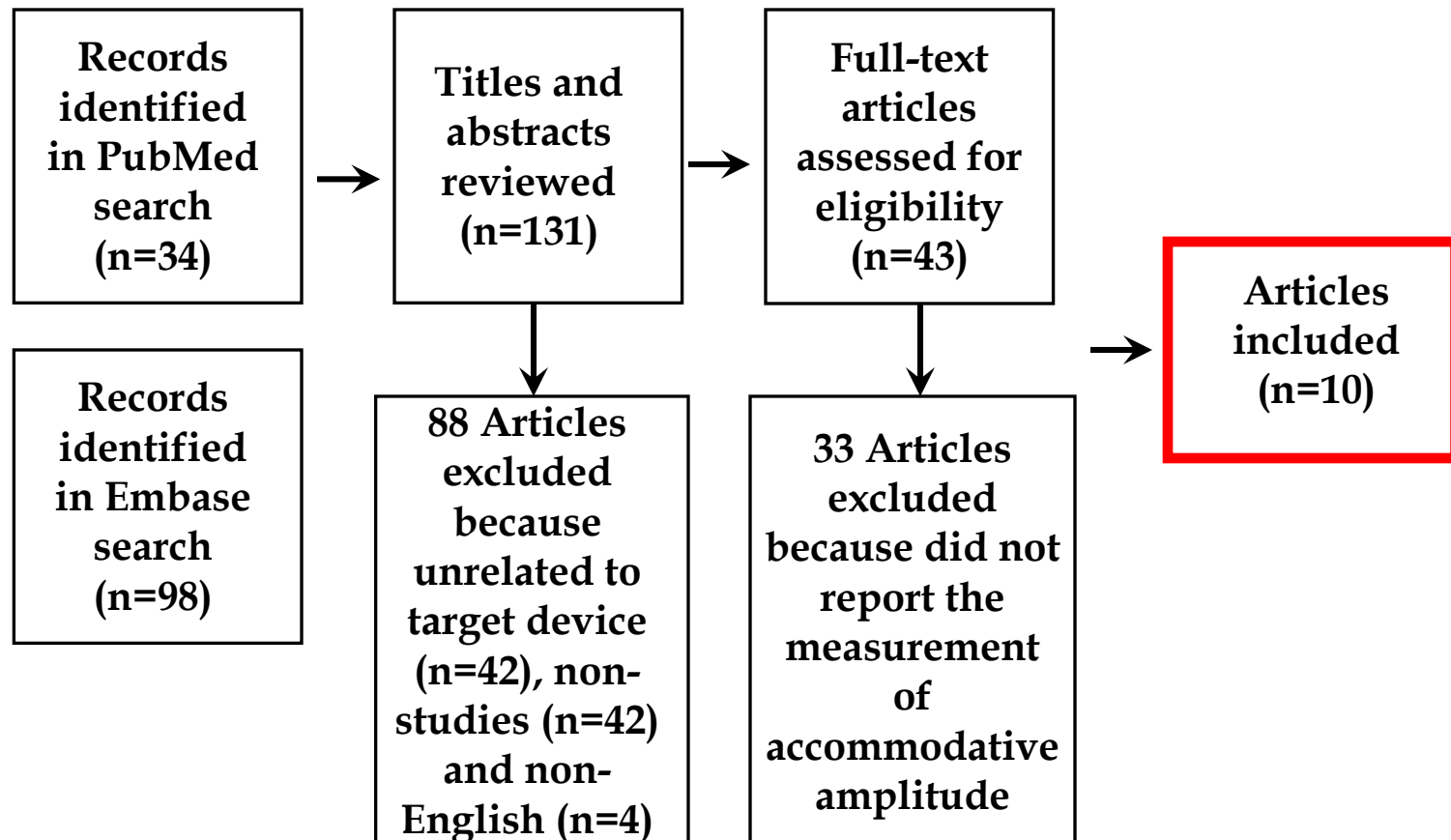


AA Assessment Comparison for Biometric Method

Crystalens HD Study	Current ANSI AIOL Draft
No Control	Control Recommended
No Masking	Recommendation to Minimize Bias
Pharmacologic Agents (6% pilo; 1% cyclo)	Use of Pharmacologic Agents Not Mentioned
Min. 3 Weeks Between Measurements (baseline & 1% cyclo then 6% pilo)	Measurement at a Single Study Visit
One Time Measurement at Each Accommodative State	Assess q6 months (up to 2 years)
Details of Methodology Not Specified in Protocol	Recommendation to Provide Thorough Description of Methodology Including Details of Instructions to Technicians and Patients
31 primary AIOL Eyes and 4 Fellow Eyes	Minimum 100 AIOL Eyes and 50 Control Eyes
No Conversion to Diopters	Recommends Validated Conversion Between Biometric and Dioptric Value

Accommodation Literature Review*

Article Retrieval and Selection



*same methods as safety literature review; however, Pubmed search updated separately on 2/7/2013 to yield an additional article in this review.

Accommodative Assessments - Literature Review

- Objective measurement types studied:
 - » changes in anterior chamber depth (ACD)
 - » optical dioptric changes using dynamic aberrometer or refractometer/autorefractor
 - » dynamic retinoscopy
- Three studies with a control:
 - » 1 using dynamic retinoscopy
 - » 1 using dynamic autorefractor,
 - » 1 using ultrasound biomicroscopy (UBM)
- Two studies used pilocarpine for near stimulation

Accommodative Assessment via Measurement of Δ ACD

Objective Technique	Author, Year	N (eyes)	Objective Measurement		Subjective Amplitude	
			Δ ACD (mean) Crystalens	Δ ACD Control	Crystalens	Control
Partial Coherence Interferometry*	Koeppel, 2005	30	no accommodation (backward movement)	--	--	--
UBM	Marchini, 2004	20	0.32 mm	--	1.08 D	--
UBM**	Marchini, 2007	~29 per arm	0.17 mm	- 0.03mm	1.19 D	1.42 D
3D Ultrasound*	Stachs, 2006	4	0.13 mm	--	--	--

Note: All studied the Crystalens AT-45

* Pilo used for near stimulation **Control = monofocal IOL; other timepoints also studied

Accommodative Assessment via Aberrometry/Refractometry

Objective Technique	Author, Year	N (eyes)	Crystalens Model	Objective Measurement (Mean Dioptric Amplitude)	
				Crystalens	Control
Hartinger Optometer*	Stachs, 2006	4	AT-45	0.44 D	--
Dynamic Aberrometer	Tahir, 2010	1	AT-52SE	No Defocus change	--
Dynamic Autorefractor**	Zamora-Alejo, 2013	~20 per arm	CrystalensHD	Negative accommodation	Negative Accommodation

* Pilo used ** Control = monofocal IOL

Dynamic Autorefractor–Measured Spherical Equivalent (Crystalens HD)

Parameter	Control Group	Crystalens Group	<i>p</i> ^b
6 meters			.800
Mean (D) ± SD	+0.05 ± 0.62	-0.03 ± 0.47	
Range	-0.92 to +1.59	-0.65 to +1.20	
50 cm			.697
Mean (D) ± SD	+0.24 ± 0.65	+0.16 ± 0.57	
Range	-0.93 to +1.98	-0.69 to +1.33	
40 cm			.027
Mean (D) ± SD	+0.45 ± 0.52	+0.07 ± 0.50	
Range	-0.29 to +1.54	-0.53 to + 0.92	

Accommodative Assessment via Dynamic Retinoscopy

Objective Technique	Author, Year	N (eyes)	Objective Measurement (Mean Dioptric Amplitude)		Subjective Amplitude	
			Crystalens	Control	Crystalens	Control*
Dynamic Retinoscopy	Macasai, 2006	112 per arm	2.42 D	0.91 D	1.74 D**	0.75 D**

Note: AT-45 Model Studied

*** Monofocal IOL control **Monocular defocus method**

Accommodative Amplitude – Available Information

- No objective or subjective accommodative assessments in the Trulign study
- DCNVA $\geq 20/40$
 - » Trulign Study: 62.9% Trulign subjects, 64.6% control subjects
 - » Crystalens Study: 90.1%
- Crystalens IOL study*
 - » 5 subjects (10 eyes)
- Crystalens HD study*
 - » Δ ACD and push down test
 - » No control, No Masking, Acc./Non-acc. states evaluated 3 wks apart
- Literature* shows mixed results
 - » AA variable depending on study methodology
 - » Results Range from Negative (backward) to Positive Acc. Movement

Question for Panel Discussion

With regard to accommodative amplitude, the following information is available:

- » No objective or subjective assessments in the Trulign study
- » 5 subjects (10 eyes) in the original Crystalens study
- » Biometry data (31 primary eyes), push down test (33 eyes) in Crystalens HD study
- » Literature shows mixed results by objective assessments (ranged from negative to positive accommodative movement)

Given the currently available information, do you believe the data support the applicant's proposed IFU of "approximately 1 diopter of monocular accommodation?"



Statistical Issues in PMA P030002/S027

Trulign Toric Accommodating Posterior Chamber Intraocular Lens

Laura Lu, Ph.D

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Office of Surveillance and Biometrics

FDA/CDRH

Outline

- Statistical analysis plan
- Main results on the primary endpoint
- Consistency of treatment effect across subgroups

Statistical Analysis Plan

- Treatment groups and randomization scheme
 - » 1:1 randomization to Toric IOL 1.25D and sphere IOL (control)
 - » Additional patients' data collected for Toric IOL 2.00D and Toric IOL 2.75D, not to be compared with Control
- Percent of the Intended Reduction in Absolute Cylinder: only endpoint to be formally compared between Toric IOL 1.25D and Control
- Subgroup analyses
 - » Not proposed in the protocol
 - » Performed post-submission: age and gender

Percent of the Intended Reduction in Absolute Cylinder at Form 4

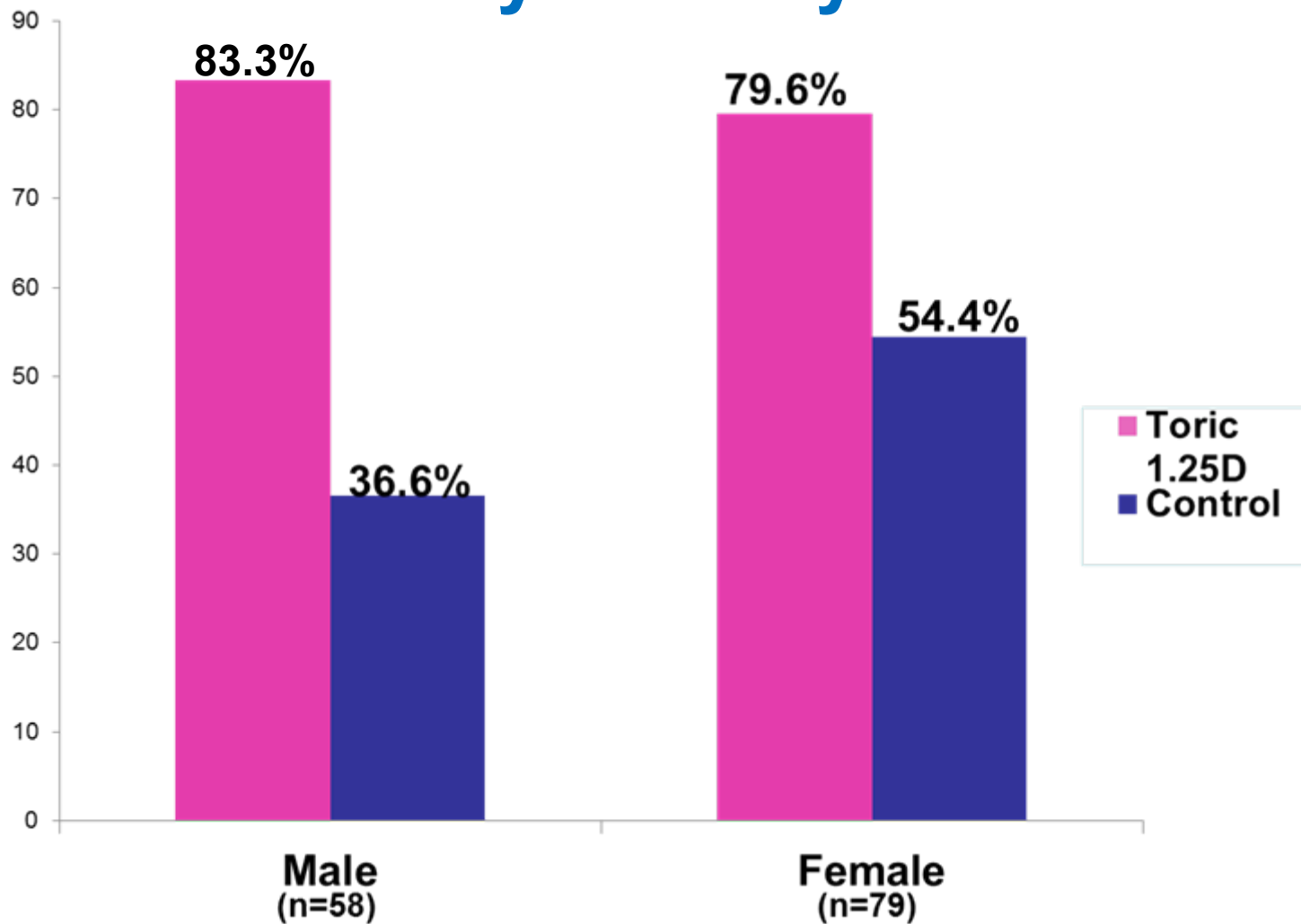
	Control (N=66)	Toric IOL 1.25 D (N=71)	Toric IOL 2.00 D (N=40)	Toric IOL 2.75 D (N=22)
Mean (%)	46.3	81.1	87.9	97.2
SD	(44.2)	(31.8)	(26.7)	(18.7)
Toric IOL 1.25D – Control (%) (95% CI)	34.7 (21.6, 47.8)			
P-Value	<0.001			

SD: standard deviation; CI: confidence interval

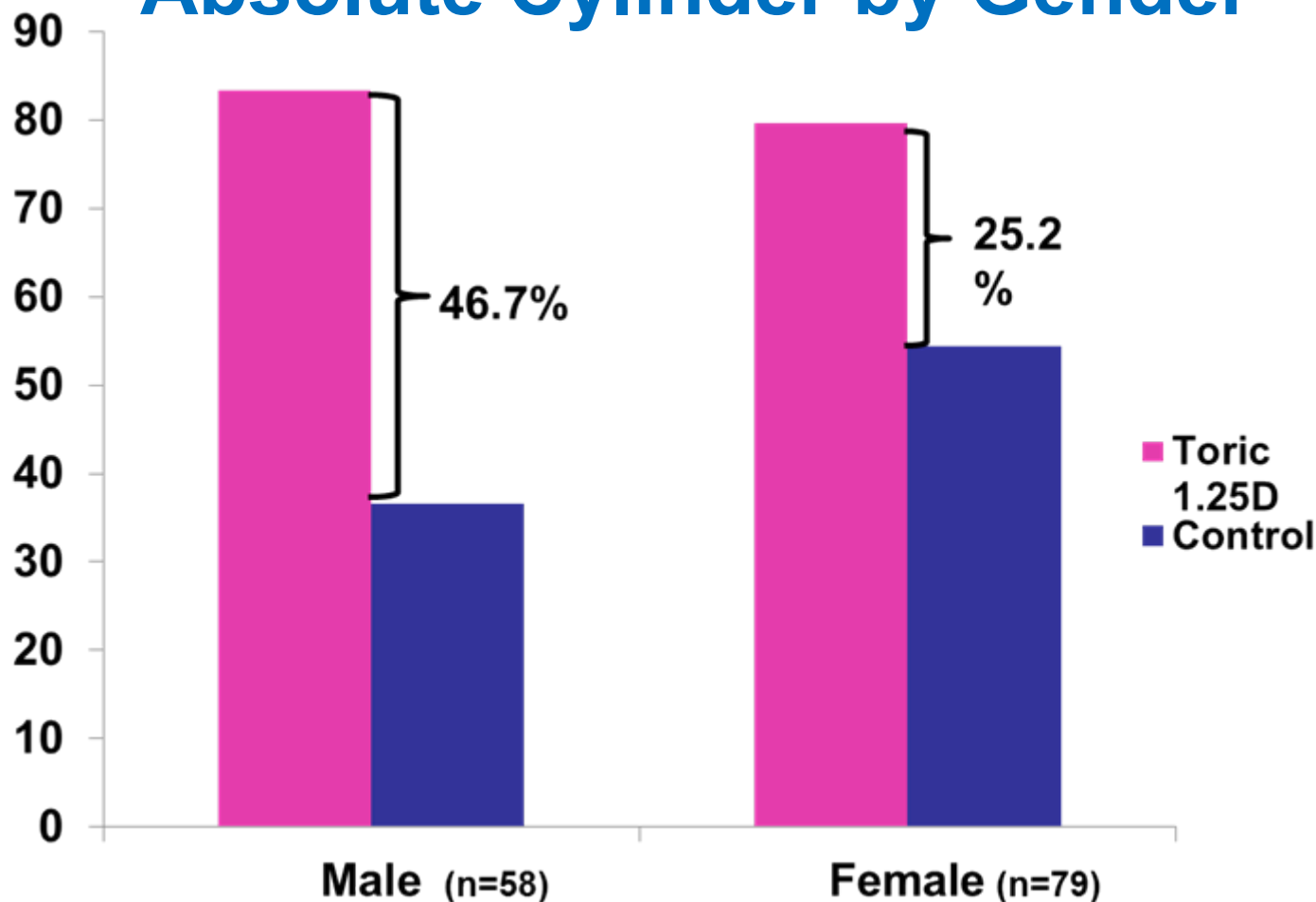
Subgroup Analyses

- Post-submission subgroup analyses:
 - » Age
 - » Gender
- Consistency of results across gender and age subgroups
 - » Clinical concern
 - » Statistical significance

Percent of the Intended Reduction in Absolute Cylinder by Gender

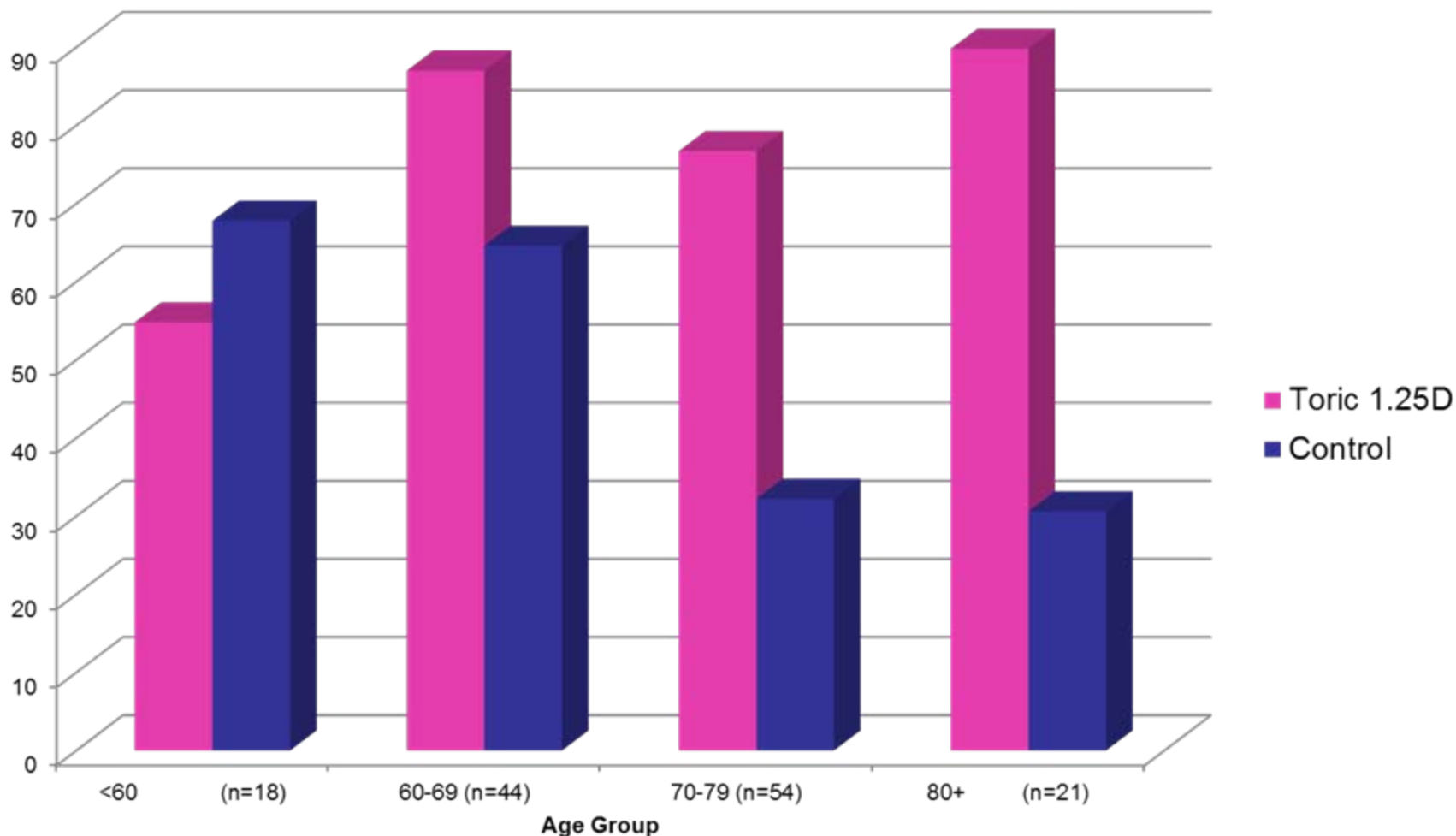


Percent of the Intended Reduction in Absolute Cylinder by Gender

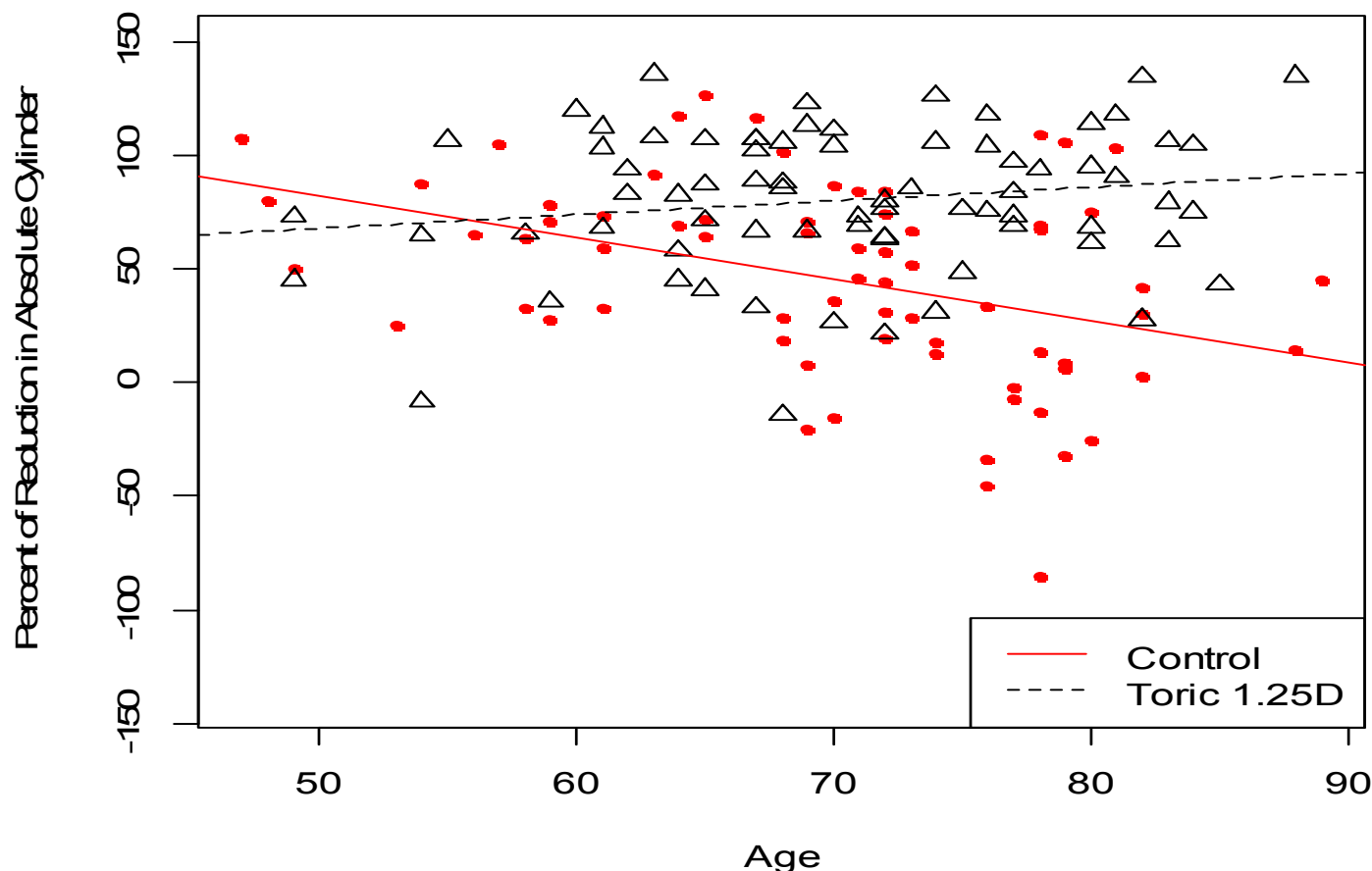


Treatment by Gender Interaction: $p=0.1043$

Percent of the Intended Reduction in Absolute Cylinder Across Age Groups



Percent of the Intended Reduction in Absolute Cylinder Along Age



Treatment by age interaction $p=0.0002$

Summary

- Treatment effects different between male and female
 - » 46.7% in male, 25.2% in female
 - » Treatment by gender interaction ($p=0.1043$)
- Treatment effect different along age
 - » Treatment effect of Toric 1.25D vs. Control decreases as age decreases
 - » Treatment by age interaction ($p=0.0002$)

Question for Panel Discussion

Below age 60, subjects implanted with the control IOL had greater percent reduction in cylinder than those implanted with the toric IOL (1.25D). In light of this, please discuss:

- a. If you believe limitations by age should be added to the Indications for Use; and
- b. What specific labeling recommendations you believe are appropriate

Post-Approval Study (PAS) Considerations

Megan Gatski, MSN, PhD

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Reminder

- The inclusion of Post-Approval Study questions should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device.
- The presence of a post-approval study plan or commitment does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether the risks outweigh the benefits.
- The premarket data must reach the threshold for providing reasonable assurance of safety and benefit before the device can be found approvable and any post-approval study could be considered.

General Principles for Post-Approval Studies

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness
- Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness

Need for Post-Approval Studies

- Gather postmarket information
 - » Long-term performance including effects of re-treatments & device changes
 - » Real-world device performance (patients and clinicians)
 - » Effectiveness of training programs
 - » Sub-group performance
 - » Outcomes of concern (safety and effectiveness)
- Account for Panel recommendations

Post-Approval Study Components

- Fundamental study question or hypothesis
- Safety endpoints and methods of assessment
- Acute and chronic effectiveness endpoints and methods of assessment
- Duration of follow-up

Applicant's Post-Approval Plan

The applicant did not provide a post-approval study plan or proposal in their premarket submission.

FDA Assessment of Postmarket Issues

- Combination of Toric and Accommodative features makes it a 1st of a kind device
- The premarket performance data does not reflect real-world device experience
 - » Highly selected centers and study population
- Evaluation of the real-world performance needed including:
 - » device safety, vaulting concern
 - » the long-term performance
 - » evaluation of performance in sub-groups

Question for Panel Discussion

- Please discuss if there is a need for postmarket evaluation of the real-world device performance, including:
 - » Appropriate study question and study design
 - » Safety/effectiveness endpoints
 - » Appropriate follow-up for long-term evaluation
 - » Need for evaluation of performance in sub-groups.